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Studies on Tetanus Immunization in the R.C.A.F.*

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THE administration of tetanus toxoid in the Canadian armed forces during the recent war presented an opportunity to study the response to this antigen on a large scale and also to measure the serum tetanus antitoxin levels in large numbers of personnel. These studies were undertaken as a joint project of the School of Hygiene, University of Toronto, and the Medical Branch of the R.C.A.F.

Blood was drawn from R.C.A.F. personnel and titrated for the level of serum tetanus antitoxin in the laboratories of the School of Hygiene. The serum antitoxin findings were studied in relation to the inoculation records. In addition, observations were made on the serum tetanus antitoxin levels in the blood of injured civilians after the prophylactic administration of tetanus antitoxin.

Scope and Method of Study

Blood was drawn** from 1,968 Air Force personnel, including men and women, ages 18-45 years and representing R.C.A.F., R.A.A.F., R.A.F. and other allied forces. The length of service varied from a few months to more than five years. A record of all tetanus immunization was extracted from their medical documents.

Preliminary tests indicated that the R.C.A.F. personnel showed consistently higher serum tetanus antitoxin levels than the personnel of other Forces. Because the antigen used in the R.C.A.F. came from a single source and the medical documentation was fairly uniform, it appeared that data

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secured from these personnel might yield information with a greater degree of homogeneity and therefore reliability. Accordingly the further titrations were limited to the sera of approximately 1,000 R.C.A.F. personnel selected so as to include all the R.C.A.F. personnel of the 1,968 whose records indicated any irregularity in their immunization process.

Until the spring of 1941, routine inoculations in the R.C.A.F. included a primary stimulus of two injections of 1 c.c. of fluid tetanus toxoid given at an interval of six weeks followed by annual reinforcing doses of 0.5 c.c. In mid-1941 the routine was changed to an initial course of three injections of 1 c.c. of T.A.B.T.* vaccine at three-week intervals and annual reinforcing doses of 0.5 c.c. (1). No untoward reactions were encountered, any fever and local reactions seen being similar to those observed with T.A.B. vaccine alone.

The primary inoculations were given almost entirely at the Manning Depots where special care was taken throughout to ensure that all personnel received their routine injections and that the medical documents were completed. In spite of this, however, as is to be expected, the documents of some of the personnel included in the study showed deficiencies. Some of these deficiencies probably indicate failure to receive toxoid; on the other hand, they perhaps indicate errors or deficiencies in recording; it is probable, too, that in the records showing toxoid administration completely in accord with the routine there would be individuals who failed to receive what the records indicated. Having in mind the care with which the inoculations were given, it is felt that these deficiencies or uncertainties are very small and in no way vitiate the general findings. Where no initial series of two or three doses at short intervals was recorded, the first dose received, even if only 0.5 c.c., and any further toxoid given within six months was considered the primary or initial stimulus; all inoculations given more than six months after the first primary stimulus were considered as reinforcing doses.

Through the co-operation of the Toronto General Hospital and the Hospital for Sick Children, Toronto, it was possible to obtain samples of blood from civilians who had been given tetanus antitoxin. The serum antitoxin level of five children admitted to the Hospital for Sick Children was measured prior to administration of 1,500 units (3,000 International units) of anti-tetanus serum and repeatedly for periods up to three weeks afterwards. A single sample of blood was taken from each of twenty-nine out-patients at the Toronto General Hospital at periods varying from one to ten days after administration of antitetanus serum.

Tetanus Antitoxin Titration Methods

The tetanus antitoxin titrations were made with mice (2). The details of the test are as follows:

**The combined typhoid-paratyphoid vaccine and tetanus toxoid (T.A.B.T.) contains 750 million typhoid bacilli, 250 million paratyphoid A bacilli, and 250 million paratyphoid B bacilli suspended in fluid tetanus toxoid. In preparing the vaccine the typhoid-paratyphoid emulsions are suspended in tetanus toxoid so that practically three doses of one c.c. fluid tetanus toxoid are administered in the course of three inoculations of T.A.B.T. The tetanus toxoid contains approximately 8 Lf's per c.c.*

Into six small test tubes 1 c.c. amounts of a dilution of tetanus toxin are distributed. To one of the tubes is added 1 c.c. of a 1:10 dilution of the serum to be tested; and into a second tube 1 c.c. of undiluted serum. To the remaining four tubes there is added 1 c.c. of standard tetanus antitoxin diluted to contain 0.007, 0.010, 0.014, and 0.020 units per c.c. respectively. The mixtures in the six tubes are thoroughly mixed and then let stand at room temperature for half an hour. Mice are then injected subcutaneously with 0.5 c.c. amounts of the mixtures. At least two mice are injected from each mixture.

The tetanus toxin used is diluted with buffered saline pH 7.5 containing 0.08 per cent gelatine. The strength of the diluted toxin is such that mice injected with the mixtures containing 0.007 and 0.010 units of antitoxin die with symptoms of tetanus; deaths from the mixture containing the 0.010 unit occur between the 3rd and 5th day. Mice which have received the mixtures containing 0.014 and 0.020 units of antitoxin live.

Results are interpreted as follows: If the mice injected with the mixtures containing the undiluted serum and the serum diluted 1:10 live, then the serum contains more than 0.1 unit of antitoxin per c.c.; if the mice which receive the mixture containing the serum diluted 1:10 die, while those which receive the mixture containing the undiluted serum live, then the serum contains more than 0.01 unit per c.c. and less than 0.10 unit per c.c.

Preliminary titrations were done at the 1/100 unit and 1/10 unit levels so as to give: less than 1/100, 1/100, 1/100 but less than 1/10, 1/10, and more than 1/10. All specimens of serum showing more than 1/10, and for which sufficient serum remained (236), were titrated to the end-point.

Results

In the documents of 1,092 R.C.A.F. personnel, there was only one, a medical officer, in whom there was no record of his receiving any toxoid. This medical officer had no (less than 1/100 unit) antitoxin. Eliminating this case leaves a total of 1,091 whose sera were tested at two levels: 1/100 and 1/10 unit. The results are shown in Table I.

It is apparent that 1,041 of the 1,091, or 95.4 per cent, had 1/10 unit tetanus antitoxin or more per c.c. of serum; that 4.2 per cent had 1/100 < 1/10; and that only 4, or 0.4 per cent, had less than 1/100 unit per c.c. The immunization records of the 4 individuals showing less than 1/100 units are summarized below:

(a) *Case 1—E.M.S.* No inoculations had been given on enlistment in 1942. Had only one dose of 0.5 c.c. of T.A.B.T. in June, 1944, six months before bleeding.

(b) *Case 2—J.L.J.* Had only one dose of 0.5 c.c. of T.A.B.T. in July, 1944, five months before bleeding.

TABLE I

TETANUS ANTITOXIN LEVELS VS. NUMBER OF STIMULI AND TIME SINCE LAST DOSE IN 1,091 R.C.A.F. PERSONNEL

INTERVAL SINCE LAST DOSE	Initial Stimuli	Without Reinforcing Doses					With Reinforcing Doses					ALL CASES					
		Number	< 1/100	1/100 < 1/10	1/10 or >		Number	< 1/100	1/100 < 1/10	1/10 or >		Total	>1/100	1/100 < 1/10		1/10 or >	
					No.	%				No.	%			No.	%	No.	%
0-6 Mos.	1	4	2	–	2	–	56	–	–	56	100.0	60	2	–	–	58	96.7
	2	0	–	–	–	–	131	–	3	128	97.7	131	–	3	2.3	128	97.7
	3	3	–	–	3	–	276	–	1	275	99.6	279	–	1	0.4	278	99.6
	Total	7	2	0	5	71.4	463	0	4	459	99.1	470	2	4	0.9	464	98.7
7-12 Mos.	1	3	–	–	3	–	36	1	–	35	97.2	39	1	–	–	38	97.4
	2	0	–	–	–	–	107	–	6	101	94.4	107	–	6	5.6	101	94.4
	3	39	–	8	31	79.5	230	–	1	229	99.6	269	–	9	3.3	260	96.7
	Total	42	0	8	34	81.0	373	1	7	365	97.9	415	1	15	3.6	399	96.1
1-2 Yrs.	1	0	–	–	–	–	14	–	1	13	92.9	14	–	1	7.1	13	92.9
	2	1	–	–	1	–	39	–	–	39	100.0	40	–	–	–	40	100.0
	3	68	–	19	49	72.1	54	–	–	54	100.0	122	–	19	15.6	103	84.4
	4	2	–	–	2	–	–	–	–	–	–	2	–	–	–	2	100.0
	Total	71	0	19	52	73.2	107	0	1	106	99.1	178	0	20	11.2	158	88.8
2-4 Yrs.	1	0	–	–	–	–	4	–	–	4	–	4	–	–	–	4	100.0
	2	2	1	1	–	–	6	–	2	4	–	8	1	3	37.5	4	50.0
	3	15	–	4	11	73.3	1	–	–	1	–	16	–	4	25.0	12	75.0
	Total	17	1	5	11	64.7	11	0	2	9	–	28	1	7	25.0	20	71.4
ALL INTERVALS	1	7	2	–	5	71.4	110	1	1	108	98.2	117	3	1	0.8	113	96.6
	2	3	1	1	1	–	283	–	11	272	96.1	286	1	12	4.2	273	95.5
	3	125	–	31	94	75.2	561	–	2	559	99.6	686	–	33	4.8	653	95.2
	4	2	–	–	2	–	–	–	–	–	–	2	–	–	–	2	100.0
	TOTAL	137	3	32	102	74.5	954	1	14	939	98.4	1,091	4	46	4.2	1,041	95.4

(c) *Case 3—F.W.M.* A laboratory assistant who had two initial inoculations, one month apart, in January and February, 1942, 34 months before bleeding.*

(d) *Case 4—J.G.H.M.* Had a course of three injections of T.A.B. in 1941 but received no tetanus toxoid. Was given doses of 0.5 c.c. of T.A.B.T. in March 1942, April 1943, and April 1944.

It is quite apparent that none of these individuals, according to the records, had had the complete routine immunization. It will be noticed in Table I, too, that others who did not have complete routine immunization nevertheless showed levels of 1/100 and even 1/10. There is little to be added to this observation; it is gratifying to find such high levels of antitoxin even after considerable intervals (up to 3 years) in such a high proportion of the personnel. This finding is, in fact, sufficient in itself to indicate that the administration of antitoxin at the time of wounding in personnel properly immunized is largely, if not entirely, superfluous. Certainly there would be little or no fear of tetanus with antitoxin levels as indicated in this table.

There were twenty-three individuals who were classed as having one original and two reinforcing doses and all but one of these (J.G.H.M.) had 1/10 unit antitoxin or more per c.c. In seventeen of these cases the original dose was 1.0 c.c. of either tetanus toxoid or T.A.B.T. In five the dosage was exactly the same as that received by J.G.H.M. (0.5 c.c. at intervals of approximately one year). In these latter the interval between the last dose and bleeding was less than six months in two instances and 7-12 months in three.

The influence of increasing the interval between the last dose and test in reducing the antitoxin level is evident in the lower levels, as indicated in the table, after the longer periods; this, too, would be anticipated and in keeping with all former observations. So, too, the influence of reinforcing or recall doses; in fact, the need for such recall doses in maintaining high antitoxin levels is clearly demonstrated in the table. This, too, is in keeping with all our knowledge.

It is of interest that one case, F.W.M., who had received only 1 or possibly 2 doses as a primary stimulus and had not had any recall doses and showed, after an interval of 34 months, less than 1/100 unit antitoxin, nevertheless responded very quickly and forcefully to one recall dose of 0.5 c.c. administered during this study (he had 1/10 unit when tested 4 weeks later). Although only one instance, this does show clearly the persistence in that individual of the influence of the primary stimulus over a considerable interval and in spite of the recognized fall in the antitoxin level. The ability to respond quickly and forcefully—in other words, a latent immunity—was still present.

Many significant comparisons suggested by Table I are not possible because the data were not tabulated to the end-point. Further, the figures in the fine breakdown are so small that they are not informative. Essential fundamentals, however, are effectively demonstrated.

The data likewise emphasize the need for reinforcing doses in maintaining high antitoxin levels. The observed differences in the proportions with anti-

**There is reason to believe that F.W.M. had only 1 dose of T.A.B.T. and not 2 as recorded.*

toxin levels of 1/10 unit or more between those with and those without reinforcing doses (Table I) are significant. In the group without reinforcing doses, there is a larger proportion with lower antitoxin levels. This, too, is in keeping with all our knowledge. The data give no indication that we need a reinforcing dose at a shorter interval than one year.

It is apparent in the table that the end-point of many of the samples was not reached by testing. In fact, it was reached only in the 4 samples with less than 1/100 unit and in the 46 samples with more than 1/100 and less than 1/10. There was enough serum in 236 samples with 1/10 unit or more to permit further titrations. The results of these titrations are shown in Table II. From the figures given in this table one can find the probable number in any antitoxin range in the groups 1/10 unit or more in Table I.

It is apparent that within the 6-month interval after the last dose over 80 per cent of the 106 tested showed 1 unit or greater. One half of those

TABLE II

SERUM ANTITOXIN LEVELS IN 236 SERA TITRATED TO THE END-POINT

Interval Since Last Dose	Antigenic Stimuli		Number	Antitoxin Titre (Units per c.c. Serum)					
	Initial	Reinforcing		$\frac{1}{10} < \frac{1}{5}$	$\frac{1}{5} < 1$	$1 < 5$	$5 < 10$	$10 < 20$	$20 < 30$
0-6 Mos.	1	0	0	–	–	–	–	–	–
	1	+	9	1	1	7	–	–	–
	2	0	0	–	–	–	–	–	–
	2	+	24	2	8	12	2	–	–
	3	0	0	–	–	–	–	–	–
	3	+	73	–	6	33	27	5	2
	1-3	0-+	106	3	15	52	29	5	2
7-12 Mos.	1	0	0	–	–	–	–	–	–
	1	+	9	1	5	3	–	–	–
	2	0	0	–	–	–	–	–	–
	2	+	17	4	9	4	–	–	–
	3	0	4	3	1	–	–	–	–
	3	+	69	2	25	35	6	1	–
	1-3	0-+	99	10	40	42	6	1	0
1-2 Yrs.	1	0	0	–	–	–	–	–	–
	1	+	2	–	2	–	–	–	–
	2	0	0	–	–	–	–	–	–
	2	+	5	1	2	2	–	–	–
	3	0	15	7	6	2	–	–	–
	3	+	4	1	2	1	–	–	–
	1-3	0-+	27*	9	12	6*	0	0	0
2-3 Yrs.	1	0	0	–	–	–	–	–	–
	1	+	1	–	–	1	–	–	–
	2	0	0	–	–	–	–	–	–
	2	+	1	1	–	–	–	–	–
	3	0	2	1	–	–	1	–	–
	3	+	0	–	–	–	–	–	–
	1-3	0-+	4	2	0	1	1	0	0
TOTAL	ALL INTERVALS		236*	24	67	101*	36	6	2

*Includes one case with four initial and no reinforcing doses.

tested showed 1 unit and less than 5, the range on each side extending from 3 showing as low as 1/10 unit less than 1/5 to 2 showing 20 less than 30 units. At an interval of 1-2 years a much smaller proportion showed as much as 1 unit, the larger proportion, 80 per cent, showing less than the 1 unit. Again, in this table, the higher levels in those receiving reinforcing doses is generally apparent.

Duration of Immunity

The data do not afford desired information on duration of immunity beyond two years. Of the 1,091 cases included, 206 had had their last stimulus more than one year before bleeding but only 28 had gone two years without a T.A.B.T. inoculation (Table I). In the nature of things this had to be the case since annual booster doses were a requirement. This limitation suggests the desirability of following up a segment at least of this group for the purpose of securing data on the persistence of immunity 3 to 5 years after the last dose of tetanus toxoid.

Antitoxin Levels Following Prophylactic Tetanus Antitoxin

In order to compare levels of antitoxin obtained by active immunization with those obtained by passive immunization measured by the same testing technique, sera were obtained from 34 individuals, 5 children and 29 adults, after receiving 1,500 units of A.T.S. The serum antitoxin levels found are presented in Tables III and IV. Antitoxin titrations done for all five children on serum secured prior to the administration of prophylactic antitoxin showed no titratable antitoxin.

It was impossible to obtain bloods on each subsequent day for any large proportion. However, of 21 adults' blood tested 24 hours after receiving the A.T.S., 3 showed 1/100 but less than 1/10, 8 showed 1/10 but less than 1/5, and 10 showed 1/5 but less than 1. The children all showed from 1/5

TABLE III

TETANUS ANTITOXIN LEVELS* IN THE SERA OF FIVE CHILDREN AFTER ADMINISTRATION OF APPROXIMATELY 1,500 UNITS A.T.S.

PATIENT AND AGE	Number of Days After Administration of Antitoxin											
	1	2	3	4	6	7	8	9	10	12	21	22
A (11)	1/5	1/5-1	1/5-1	1/5-1	–	–	–	–	–	–	–	–
B (12)	1/5-1	1/5-1	1/5-1	1/5-1	–	1/100 -1/10	–	$<\frac{1}{100}$	–	–	–	–
C (?)	1/5-1	1/5-1	1/5-1	1/5-1	1/5-1	–	1/5-1	–	1/5-1	1/5	–	1/100 -1/10
D (7)	1/5-1	1/5-1	1/5-1	1/5-1	1/5-1	–	–	1/5-1	1/5-1	1/5	–	1/100 -1/10
E (3)	1/5-1	1	1-5	1-5	1/5-1	–	1/5-1	–	1/5-1	1/5-1	1/100 -1/10	

*Tetanus antitoxin levels are recorded in the table in units of tetanus antitoxin per c.c. of serum, e.g. "1/5-1" means "1/5 unit but less than 1 unit of antitoxin per c.c. of serum."

TABLE IV

TETANUS ANTITOXIN LEVELS IN THE SERA OF TWENTY-NINE ADULTS AFTER ADMINISTRATION OF APPROXIMATELY 1,500 UNITS A. T. S.

TETANUS ANTITOXIN (units per c.c. of serum)	Interval Between Administration of Antitoxin and Bleeding			
	1 day	2 to 7 days	10 days	TOTAL
Less than 1/100	–	–	1	1
1/100 but less than 1/10	3	–	–	3
1/10 but less than 1/5	8	3	2	13
1/5 but less than 1	10	2	–	12
TOTAL	21	5	3	29

to 1. By the 7th day one of the children (the only one tested) had dropped to 1/100 to 1/10 and by the 9th day this child, a 12-year-old, showed less than 1/100. Three children tested on the 21st or 22nd day still retained 1/100 to 1/10. Of 3 adults tested on the 10th day, 1 showed less than 1/100 and 2 showed 1/10 but less than 1/5 unit.

It is apparent, therefore, that the antitoxin levels induced by the active immunization procedures indicated often far exceeded the levels obtained by passive immunization and that even with lesser active immunization and after extended intervals the antitoxin levels persistently were on the whole fairly comparable with the levels found following passive immunization in adults for the short period of 7 to 10 days.

Wartime Tetanus Experience

In the R.C.A.F., one fatal case occurred and no others were reported (3). This case had had three doses of T.A.B.T. at intervals of 19 days and two weeks respectively in October-November, 1942, and one reinforcing dose of 0.5 c.c. on October 25, 1943, ten months before injury. The following is a summary of this case:

> Crushed tip of left third finger severely in a door on 1st September, 1944. Wound dressed, three sutures, and 3,000 International units of tetanus antitoxin and 13,000 units of anti-gas gangrene serum given intramuscularly. Local infection developed in left thigh at site of inoculation on fifth day. On 10th September stiffness of jaw and neck appeared, with pain on swallowing. Transferred to E.M.S. hospital same day and diagnosis of tetanus made. Patches of urticaria over body. After desensitization, was given 1,500 British units of A.T.S. intravenously. Developed anaphylactic reaction after 5 c.c. A.T.S. intravenously. Responded to adrenalin. Wound was opened and sections sent to laboratory. Given 60,000 B.U./A.T.S. intramuscularly. On 11th September was given 20 c.c. A.T.S. intramuscularly. Had two tetanus convulsions 25 and 40 minutes later. Died at 4: 40 a.m. on 12th September 1944.

A total of 155,500 International units of tetanus antitoxin was given. Time from injury to development of trismus was eight days and five hours. R.A.F. specialists thought excision of wound might have flooded the body with toxin. Suggested possibility of septicaemia but there was considerable evidence against this.

Summary

1. The administration of tetanus toxoid as carried out in the R.C.A.F. yielded a remarkably high proportion (99.6 per cent) of personnel with 1/100 unit or more of antitoxin per c.c. None of 4 exceptions (0.4 per cent) had received the routine course of inoculations.

2. Antitoxin levels of 1/100 unit per c.c. or more were found in over a hundred individuals who had escaped the initial course but had received two or more annual single injections.

3. The administration of reinforcing stimuli was so well carried out that our experience does not provide a definite answer regarding the duration of immunity. However, of twenty-eight persons who had been over two years without a stimulus, only one failed to show 1/100 unit per c.c. or more of antitoxin in the serum. In this case only two original stimuli (possibly one) had been given and these had not been followed by any reinforcing doses.

4. The influence of increasing the interval since the last dose on the antitoxin level, and the need for recall doses in maintaining a high antitoxin level, are demonstrated.

5. The persistence of the influence of the primary stimulus and the ability to respond quickly to toxoid even at long intervals thereafter, was demonstrated.

6. The highest tetanus antitoxin levels were found in those persons who had received three initial and one or more reinforcing stimuli and who were bled within six months of the last stimulus.

7. The antitoxin levels induced by the active immunization procedures in Service personnel often far exceeded the levels obtained by passive immunization.

8. The administration of tetanus antitoxin at the time of wounding in personnel properly immunized is largely, if not entirely, superfluous.

Acknowledgment

This study was made possible by the co-operation of many individuals and groups. Special acknowledgment is made of the assistance offered by the staff of the School of Hygiene, University of Toronto, who suggested the study and provided laboratory facilities for carrying it out, and of the advice and supervision of the technical work afforded by Dr. P. J. Moloney and Dr. D. T. Fraser.

The careful, earnest work of the R.C.A.F. technicians, clerks, and hospital assistants played an essential part in the successful completion of these studies. The contribution of Cpl. W. R. Barnes is worthy of particular note.

F/L. J. B. Hardie, officer in charge of Medical Statistics, Institute of Aviation Medicine, Toronto, assisted in the preparation of the statistical tables and in the checking of original documents.

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Experimental Studies on Rabies Virus

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THE most effective weapon against rabies is prophylactic vaccination of domestic animals. This is especially true for areas where rabies among wild animals occurs either in enzootic or epizootic form, thus maintaining a constant source for the dissemination of rabies to domestic animals. The role of the dog as a major link in the transmission of rabies to humans has been recognized for many years, but the importance of wild animals should not be underrated, not only as a hazard to domestic animals, but also as a source of danger to man. Bites by rabid wolves or foxes are not infrequently reported and in general the prognosis is not favorable. The various factors which have impeded progress in applying mass vaccination to the canine population may be listed in the following order: the necessity for multiple vaccinations; the occurrence of postvaccinal neuroparalytic accidents; the high cost of production of the vaccine; and, last but not least, the lack of proper understanding of the problem on the part of the general public.

Whereas no one doubts the efficacy of killed phenolized rabies vaccine as a prophylactic agent, the duration of the immunity conferred remains debatable. Time does not permit a review of the data accumulated on this subject, but it may be mentioned that Johnson (1), in his study of vaccinated dogs challenged with street virus, observed mortality figures ranging from 4 to 25 per cent among the vaccinated dogs, as compared to 55 and 66 per cent in the control animals.

In the United States, in general, veterinarians advise that dogs be vaccinated against rabies once a year. Were a vaccine available which, with a single injection, would confer immunity to the animal for its normal life-span, it would greatly facilitate the achievement of mass vaccination of the canine population. In regard to neuroparalytic accidents, apart from isolated instances described in literature, there is little concrete evidence that postvaccinal paralysis occurs in dogs. However, recently Jervis, Burkhardt and I (2) had occasion to observe postvaccinal paralysis in four animals among the 90 dogs of the Saint Bernard and Great Pyrenee breeds which had been given a single 10 c.c. injection of phenolized 20 per cent horse-brain rabies vaccine. Four of the Great Pyrenees became paralyzed 14 to 17 days after the inoculation; one died before any studies were performed, but two of the dogs were sacrificed when moribund. No infec-

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Findings reported in this paper represent, in some instances, work still in progress and therefore some of the results should be considered as of a preliminary nature. A more extensive report based on complete results is to be published in the future.

tious agent was recovered from their central nervous tissues by subinoculation into dogs, mice and guinea pigs. Histopathological lesions were similar to those described in human cases of postvaccinal paralysis, and in the so-called isoallergic encephalitis in monkeys. The fourth dog is now recovering from the paralysis but probably some sequelae will remain. It is difficult to draw any inferences from the above observation, such as that this particular breed is hypersensitive to inoculation of brain tissue, or that the incidence of 4 out of 90 dogs could be applied statistically to the entire dog population vaccinated against rabies.

The need for an efficient "single injection" method of immunization of dogs, and the occurrence of postvaccinal paralysis, motivated the studies reported herein. The egg-adapted Flury strain of rabies virus, chosen for this particular study, was isolated by Leach and Johnson (3) from the spinal cord of a child who had died after rabies infection, and by inoculation into the brain of 1-day-old chicks was passaged serially by Dr. Johnson. The virus was received at the 136th passage-level, passed through two additional chick brain passages, and then the infectious material was transferred serially by inoculation into yolk sacs through 90 egg generations. Three additional strains, of minor importance for this presentation, were adapted to the embryonated hens' eggs. These will be referred to as the NIH strain (rabbit-brain fixed strain of rabies virus passed through 70 egg passages), the NYC strain (street strain obtained from infected salivary gland of a dog in New York City and passed through 65 egg passages), and the Zillwood strain (obtained from the central nervous tissue of a British soldier infected in India and passed through 10 egg passages).

Since the Flury strain showed the most promise for the development of a vaccine which would meet the requirements set above, some of the characteristics of this strain will be described briefly (4). Even in the course of the early egg passages it was observed that the Flury strain differs in its pathogenicity from other "fixed strains" of rabies virus. The Flury strain remained pathogenic for mice, cotton-rats, hamsters and guinea pigs inoculated intracerebrally, and the results of titrations were fairly uniform and constant. Positive results by the intracerebral route could be obtained in rabbits only with difficulty and no virus could be recovered from brain tissues of animals which died after inoculation with the 10^{-1} dilution of embryo suspension; intramuscularly it showed no pathogenic properties for rabbits even at various egg-passage levels. Guinea pigs inoculated extraneurally, although slightly susceptible to the low egg-passage levels of the Flury strain, became almost completely refractory to the higher level passages. Only occasionally did one animal out of ten inoculated with the 20 per cent suspension of infected embryos show any signs of paralysis. Conversely, the immunity response of the surviving guinea pigs, subsequently challenged with street virus (NYC and Zillwood strains), was excellent.

This may be best illustrated by the results shown in Table I. In these experiments guinea pigs were given intramuscularly 1.0 c.c. of lyophilized suspensions of embryos infected with the Flury strain, in decreasing twofold and fourfold dilutions. At certain intervals after vaccination all of the inoculated animals, and groups of nonvaccinated controls, were challenged intramuscularly with a 10 per cent suspension of canine salivary gland infected with street strain

TABLE I

IMMUNIZATION OF GUINEA PIGS WITH CHICK-EMBRYO ADAPTED FLURY STRAIN RABIES VIRUS

Vaccine		Challenge With Street Virus*								
Egg Passage	LD_{50} Titre in Mice	Post-vaccination	Virus Strain	Mortality Ratio of Guinea Pigs Immunized with dilutions of vaccine: 1:5	1:10	1:20	1:40	1:80	1:320	1:1280	Controls
		days									
75	1:562	29	NYC	0/8	0/8	0/7	0/9	0/6			9/9
77	1:1000	47	NYC	0/9		0/7		1/10	4/5	0/9	8/8
86	1:400	45	NYC	0/10		0/10		1/10	0/10	6/10	9/9
74	1:630	45	NYC	0/10		0/10		5/10	5/10	10/10	10/10
74	1:630	45	Zillwood	0/10		0/10		2/10	4/9	7/10	10/10

*10 per cent canine salivary gland injected intramuscularly.

of rabies virus. The results indicate that while there was a 100 per cent mortality among the control animals, the vaccinated guinea pigs showed a high degree of resistance. The only notable exception was observed in animals immunized with the 1:320 dilution of vaccine, representing the 77th egg passage of the virus. However, in view of the fact that all of the guinea pigs vaccinated with the 1:1280 dilution of the same vaccine survived the challenge inoculation, the following explanation may be offered for this apparent discrepancy. About one week after vaccination an intercurrent streptococcal infection killed 5 of the 10 guinea pigs vaccinated with the 1:320 dilution, and the survivors, which were kept in the same cage, may have suffered from the infection in a latent form which interfered with the immunological response.

Encouraged by the results obtained in guinea pigs, experiments were outlined to determine the susceptibility of dogs to this avianized strain of virus. The results are summarized in Table II. Dogs which received the intramasseter inoculation of a 20 per cent embryo suspension survived the one-year observation period without having shown any signs of illness. Similarly no signs of illness were observed in the animals which had been inoculated in the muscles of the hind legs with 5.0 c.c. of the virus, or by the intramasseter route with the 40 per

TABLE II

PARENTERAL INOCULATION OF DOGS WITH THE CHICK-EMBRYO ADAPTED FLURY STRAIN RABIES VIRUS

Egg Passage	Route	Volume	Number of Dogs		Observation Period
			Died	Survived	
		ml.			*months*
22	Intramasseter	0.5* × 2	0	5	12
22	Intramasseter	0.1* × 2	0	5	12
22	Subcutaneous	5.0*	0	15	3
40	Intramuscular	5.0*	0	9	2
74	Intramasseter	0.2** × 2	0	4	6
74	Intramuscular	5.0**	0	4	6

*20 per cent suspension of infected embryos.
**40 per cent suspension of infected embryos.

cent embryo suspension. Repeated experiments confirmed the observation that the Flury strain given parenterally is innocuous for the canine species.

With these favorable results in hand, the next task was to determine the immunizing power of the Flury strain in dogs. The results are shown in Table III. Dogs were given, in the muscles of the hind legs, a single 5 c.c. injection of either a 20 or 40 per cent suspension of infected embryos at various egg-passage levels, and then challenged at different intervals by bilateral intramasseter inoculation with a 10 per cent suspension of canine salivary gland infected with the NYC street strain of rabies virus (LD_{50} titre in mice $10^{-4.50}$ to $10^{-6.15}$). The vaccine consisted of either fresh or lyophilized preparations and this may partially explain the differences in LD_{50} titres in mice among the several

TABLE III

IMMUNIZATION OF DOGS WITH CHICK-EMBRYO ADAPTED FLURY STRAIN RABIES VIRUS

Vaccine		Challenge with NYC Street Virus		
Egg Passage	LD_{50} Titre in Mice	Postvaccination	Mortality Ratio of Dogs	
			Vaccinated	Controls
		weeks		
36	$10^{-5.50}$	5	0/6	3/6
40	$10^{-3.65}$	9	0/9	8/15
40	$10^{-4.0}$	7	0/10	9/10
74	$10^{-4.75}$	5	0/6	3/6
74	$10^{-4.75}$	27	0/4	9/10
75	$10^{-3.75}$	5	0/5	3/6
77	$10^{-3.00}$	7	0/10	9/10
80	$10^{-2.60}$	5	0/6	3/6
84	$10^{-2.50}$	7	2/10	9/10

lots of vaccines. The results of the inoculation with the street virus of the non-vaccinated control animals confirm the observations of numerous investigators, namely, that there is a certain degree of resistance in dogs to street virus and, therefore, in individual experiments the results of the challenge inoculations of vaccinated dogs may be of lesser statistical significance. Nonetheless, it is of interest that in a total of 66 dogs vaccinated with the Flury strain only 2 succumbed to the massive challenge-inoculation, whereas 23 of the 37 control dogs died. These two animals belonged to a group of ten dogs immunized with material obtained at the highest tested egg-passage level of the Flury strain. Furthermore, the LD_{50} titre in mice of this particular preparation was the lowest one obtained. Whether these two factors exerted any influence in lowering the immunizing potency of this particular batch of vaccine remains to be seen in future experiments.

The duration of immunity in dogs, following vaccination with the Flury strain, is now under study. The results of these experiments, together with a study on vaccination of dogs under field and not laboratory conditions, will finally determine whether the egg-adapted Flury strain fulfills the conditions set for an ideal animal rabies vaccine. Thus far, barring unexpected accidents, all the results point to a favorable outcome of the experiment.

After this discussion of canine vaccination, it is pertinent to consider briefly the problem of protecting humans against rabies. Two problems again confront us: the questionable value of the Pasteur treatment in cases severely bitten by rabid animals, and postvaccinal paralysis. It may suffice to say that there is no evidence in favor of the Pasteur treatment in cases of humans whose exposure to rabies is so severe that the incubation period is less than 30 days (5). Furthermore, evidence points overwhelmingly to the fact that the Pasteur treatment is associated with the so-called neuroparalytic accidents. The incidence of postvaccinal paralysis in the United States is believed to be not greater than one in 5,000 vaccinated persons, and yet in Los Angeles County during the 1940-45 period, an incidence of one in 1,194 treated persons was recorded (6). If we take into consideration that in the United States approximately 150,000 persons are reported annually to have been bitten by dogs, and that 30,000 of these individuals received Pasteur treatment, then the conclusion is inescapable that many persons who probably would not have developed rabies were exposed to the danger of postvaccinal neuroparalysis. It was this consideration which directed the studies towards two major goals: (a) to identify the paralitogenic factor in normal brain tissue, and if successful to purify the currently employed rabies vaccines; (b) in case of failure, to develop a procedure which would be fully as effective as the Pasteur treatment but would not carry with it the danger of neuroparalytic accidents.

Time will not be taken to give details of the studies and the negative results obtained in the experiments to determine the factor or factors responsible for the paralitogenic properties of normal brain tissue, but a brief description of the substitute developed for Pasteur treatment, namely antirabies serum, is pertinent.

Potent antirabies serum was obtained from rabbits by repeated injections of the egg-adapted Flury strain and rabbit-brain fixed viruses. Pools of the rabbit plasma were then fractionated by sodium sulfate precipitation and the fractions containing the beta- and gamma-globulins concentrated. This concentrate, when submitted to the intracerebral neutralization test in mice, was found to neutralize about 10,000 LD_{50} of fixed strain of rabies virus. The experiments on the protective power of the concentrate were conducted along the lines paralleling those encountered in nature, that is, first infection with the street virus, followed by treatment. The virus-inoculum consisted of suspensions of canine salivary glands infected with the NYC street strain of rabies virus. This inoculum, in general, gave mouse intracerebral LD_{50} titres of $10^{-4.5}$ to $10^{-6.0}$, which were almost consistently reproducible in hamsters inoculated simultaneously by the bilateral intramasseter route (0.06 c.c. of respective dilution) and into muscles of hind legs (0.1 c.c.). Thus, the procedure may be considered as being equivalent to a very severe exposure, surpassing in severity that encountered by humans in nature.

The data in Table IV indicate that a direct relationship exists between the dilution of antiserum used and the amount of virus present in the infecting inoculum—that is, serum in 1:2 dilution protected 6 of the 8 animals infected with the 1:160 dilution of virus; serum in 1:4 dilution did not protect all of the animals infected with the above dilution but did save all of the animals infected

TABLE IV

SERUM PROTECTION AGAINST EXPERIMENTAL RABIES IN HAMSTERS

Serum Dilution*	Mortality Ratio of Hamsters Inoculated with Virus Dilutions:						
	1:40	1:160	1:640	1:2560	1:10,240	1:40,960	1:163,840
1:2	7/8	2/8	1/8				
1:4	8/8	6/8	0/8				
1:8		5/8	3/8	2/8			
Controls			8/8	8/8	8/9	8/9	2/9

*Antiserum administered 24 hours after virus inoculation.

with the 1:640 dilution; and, finally, dilution of 1:8 of antiserum seemed to have some protective power against the 1:160 dilution of the virus, but definite protection was shown against the 1:640 and 1:2560 dilutions. In this experiment antiserum was administered 24 hours after infection.

In Table V the effect of delayed administration of serum following infection is presented. Against the larger infecting dose of virus (1:160 dilution) the protective power of serum, regardless of dilution employed, was evident only when the latter was administered not later than 24 hours after infection. Conversely, if less virus, though still sufficient to kill all of the control animals, was present in the inoculum, the undiluted serum was still effective when injected as late as 72 hours after infection, whereas the limit of effectiveness of the 1:4 dilution of serum was apparent 24 hours after infection.

Hamsters which survived in the above two experiments were held under constant observation for 5 months. In view of the fact that no changes took place in the survival ratio even during such a long observation period, the efficiency of serum protection seemed to be quite evident.

A comparison between the protective power of antiserum and of phenolized antirabies vaccine was next in order. The results of two experiments are shown in Table VI. It may be observed in Experiment 1 that a single injection of antiserum, in the dilution shown, protected the majority of the virus-inoculated hamsters. Conversely, treatment with vaccine, in a dilution which was calculated

TABLE V

SERUM PROTECTION AGAINST EXPERIMENTAL RABIES IN HAMSTERS AT VARIOUS TIME INTERVALS AFTER STREET VIRUS INOCULATION

Virus Dilution	Antiserum After Virus Inoculation	Mortality Ratio of Hamsters			
		Treated with Dilutions of Antiserum			Controls
		Undiluted	1:2	1:4	
1:160	*hours* 24 48	2/8 8/8	3/8 7/8	3/8 7/8	8/8
1:640	24 48 72	2/10 4/8 3/8	1/9 3/8 7/8	3/7 6/8 6/8	8/8

on the weight basis as corresponding to Pasteur treatment of humans, failed to protect even a single animal of the ten infected.

In the second experiment two types of vaccine, the so-called veterinary type prepared from infected, phenolized horse-brain tissue, and the human Semple type of vaccine, were employed. Massive doses of vaccine, administered to hamsters 24 hours after infection with the virus, again gave no evidence of protection in animals infected with the 1:640 and 1:2560 dilutions of virus. On the other hand, a single injection of antiserum, either undiluted or in 1:2 dilution, protected the majority of the animals infected with the 1:640 dilution of virus, and antiserum

TABLE VI

COMPARATIVE PROTECTION OF HAMSTERS INOCULATED WITH ANTISERUM OR PHENOLIZED RABIES VACCINE

Exp. No.	Type of Protective Treatment*	Dilution	Mortality Ratio of Hamsters Inoculated with Street Virus Dilutions					
			1:60	1:640	1:2,560	1:10,240	1:40,960	1:163,840
1	Antiserum	Undiluted	3/10					
		1:4	2/9					
	Veterinary Vaccine**	1:5000	10/10					
	Controls		9/10					
2	Antiserum	Undiluted		3/9				
		1:2		1/7				
		1:8			3/9	2/10		
	Veterinary Vaccine**	1:20		9/10	6/9	2/10		
		1:100		9/9	7/10	1/9		
	Human Vaccine**	1:20		10/10	8/10	2/9		
		1:100		10/10	6/10	3/10		
	Controls			10/10	9/10	6/10	2/9	2/8

*Treatment started 24 hours after inoculation with street virus.
**Subcutaneous daily injections with 0.5 ml. for 14 consecutive days.

in 1:8 dilution showed the same protective value for animals infected with the 1:2560 dilution of the virus. Moreover, the incubation period (time from virus inoculation until death of the animal) in the serum-treated hamsters was longer than 71 days, whereas the incubation period in vaccine-treated hamsters was much shorter, varying between 11 and 42 days. Although the data may not be statistically of great value, a suggestion of some protective power of vaccines, but not greater than that of a single injection of serum in 1:8 dilution, is apparent in hamsters inoculated with the 1:10,240 dilution of virus. However, the "heroic" treatment of hamsters with high concentrations of vaccine used in the experiment, is definitely not reproducible in humans on a weight basis, thus excluding the possibility of utilizing such vaccine treatment in human cases of rabies.

In a further effort for a critical re-evaluation of the protective power of the Pasteur treatment, an experiment was performed in which the State of Georgia vaccine, containing rabbit-brain fixed rabies living virus, was employed. As

TABLE VII

COMPARATIVE PROTECTION OF HAMSTERS WITH ANTISERUM AND LIVING VIRUS VACCINE

Type of Protective Treatment	Dilution	Number of Injections		Mortality Ratio of Hamsters Inoculated with Street Virus
		Prior to Infection	After* Infection	1:640 dilution
Antiserum	1:2		1	1/9
Vaccine**	1:6	7		4/5
Vaccine**	1:6		14	8/9
Controls				9/9

*Antiserum or vaccine treatment begun 24 hours after infection.
**State of Georgia living virus vaccine, containing fixed rabies living virus; LD_{50} titre approximately 1:570 in mice.

shown in Table VII, one group of hamsters was given vaccine for 14 days starting 24 hours after infection, while in a second group hamsters were vaccinated each day for 7 days prior to infection with street virus. Again the results indicate a complete lack of protective power of the living virus vaccine, when compared to the one injection of antiserum.

In conclusion, basing my opinion on the results obtained in the experiments just reported, I would venture to state that in hamsters vaccination after exposure to rabies is of little avail. It may be possible that in humans, because the incubation period may exceed 30 days, timely vaccination could aid in building up the protective antibody power of the individual and save him from rabies. This condition, however, cannot be reproduced in hamsters in which the incubation period (time from infective inoculation and first appearance of symptoms) varies between 13 to 22 days. In my opinion, the general evidence in favor of serum treatment is so conclusive, especially as the danger of neuroparalytic accidents following serum treatment does not exist, that a thorough field trial of serum prophylaxis in rabies is fully warranted.

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Histoplasmin Sensitivity*

PRELIMINARY OBSERVATIONS IN A GROUP OF SCHOOL CHILDREN IN THE PROVINCE OF QUEBEC

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IN 1906, E. T. Darling (1), in Panama, described three cases of a new disease whose etiology he attributed to a protozoon. This infection was characterized by the presence in the lungs of tuberculous formations as well as necrotic lesions in the liver, the spleen, and the lymphnodes. The mycotic etiology of the process was defined by Da Rocha-Lima (2), in 1913, and by DeMonbreun (3), who succeeded in isolating the agent, *Histoplasma capsulatum*, in the blood and the spleen of the patients. This infection was considered a rarity until 1944 and was encountered only in the sub-tropical regions. In a recent publication, Curtis and Grekin (4) found mention in medical literature of only 83 cases of histoplasmosis: 13 cases from 1906 to 1937 and 70 cases from 1934 to 1945. The majority are clinical cases, mostly fatal.

The improvement of diagnostic procedures, notably of proper culture media and particularly the use of specific skin tests, with antigens obtained from filtrates of *Histoplasma capsulatum*, perfected by Van Pernis, Benson and Hollinger (5) and by Zarafonetis and Lindberg (6) working independently, has shown the relatively frequent incidence of sub-clinical forms of histoplasmosis. The extension of mass radiologic examinations of the chest has brought into focus the important number of pulmonary calcifications in subjects non-allergic to tuberculin but showing hypersensitivity to intradermal histoplasmin. This subject is of especial interest in the differential diagnosis of pulmonary tuberculosis. The papers (7, 8, 9) read before the Fourth International Congresses on Tropical Medicine and Malaria have confirmed these assertions. They have outlined the geographical extension of histoplasmosis. Cases have been reported as far north as the State of New York but we found no report concerning its incidence in Canada.

Prior and Allen (10) have recently published a study on the geographical origin of freshmen students of the University of Ohio and student nurses in the hospitals of Columbus who were negative reactors to tuberculin but gave a positive reaction to histoplasmin and revealed pulmonary calcifications.

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The authors pay a tribute to Charles Edward Smith, who first demonstrated that the geographical origin of those showing calcification corresponded to the endemic distribution of histoplasmosis. The survey of Prior and Allen includes 5,087 students tested with tuberculin and histoplasmin at one and the same time. Positive reactions to histoplasmin are more frequent in males than in females. The percentage of positives to the mycotic antigen, established for each of the 88 counties of the State of Ohio, increases from east to west and from north to south. The survey also revealed that the percentage of positive reactors is definitely higher among students of rural origin than in city dwellers.

Among more recent publications, mention should be made of the work of Sontag and Allen (11). By repeated tests every six months, these authors followed the conversion to tuberculin, histoplasmin and other mycotic antigens, as well as the appearance and evolution of pulmonary calcifications, in a group of 200 children. The animal factor in the etiology of human histoplasmosis has been studied by De Monbreun (3), Birge (12), Callahan (13), Olson (14), Para (15), Seibold (16), and Tomlinson (17), who observed natural infection in dogs, and by Emmons (18) and Sangiorgi (19), who demonstrated that wild rodents were infected with histoplasmosis.

The growing interest in mycotic diseases, due to a better and more general awareness of endemic areas, has led us to search for histoplasmosis in the Province of Quebec.

In the school of a small city, located some 30 miles from Montreal, we were afforded the opportunity, while carrying out serial tuberculin testing (up to 5 mgm. tuberculin P.P.D.) in view of B.C.G. vaccination, to test the children at the same time with a solution of histoplasmin 1/1000. All children positive to tuberculin and histoplasmin had chest radiography immediately following the tests. Detailed results of the skin tests are included in Table I. The total number of children was 75, ranging in age from 6 to 15 years.

TABLE I

RESULTS OF SKIN TESTS

Negative to tuberculin and histoplasmin	Positive to tuberculin and negative to histoplasmin	Negative to tuberculin and positive to histoplasmin	Positive to tuberculin and histoplasmin
40 (53.3%)	15 (20%)	10 (13.3%)	10 (13.3%)

Total number positive to tuberculin: 25 (33.3%)
Total number positive to histoplasmin: 20 (26.7%)

The results of the chest radiographies are tabulated in Table II.

TABLE II

INCIDENCE OF PULMONARY CALCIFICATIONS

Total number X-rayed		Positive to tuberculin and histoplasmin		Negative to tuberculin and positive to histoplasmin	
Absent	Present	Absent	Present	Absent	Present
11	9	4	6	7	3

It is interesting to note that the histoplasmin reactions were intense, 3+, 9++, 8+++, when using the same standards of reading as used for Tuberculin P.P.D. tests. The number of children surveyed is rather small, but brings into focus the interesting finding that histoplasmosis is certainly valuable in the differential diagnosis of pulmonary calcification in this restricted sector of the Province of Quebec. Canadian medical literature lacks evidence that it has any serious pathologic importance. At present, there is almost general agreement that a positive reaction to histoplasmin has the same significance as the tuberculin reaction, indicating present or past infection. That pulmonary calcification may follow deep mycotic infections has also been proved (20, 21, 22, 23, 24, 25, 26). From this preliminary report, the conclusion may be drawn that further studies are urgently needed in the Province of Quebec and elsewhere in Canada, to clarify the exact locations of endemic areas. Specific antigens obtained from the infected areas should be made available. We have in mind to confirm the presence of *Histoplasma capsulatum* in subjects and animals in contact with positive histoplasmin reactors. We shall also extend this survey to northern parts of the Province of Quebec and continue our research in the county initially tested. The relation of histoplasmin infection to histoplasmin disease will be studied further by serologic reactions such as complement-fixation tests (27, 28, 29), which have some value in the diagnosis of the activity of the disease. At the same time, histoplasmosis in domestic as well as in wild animals will be investigated (30).

Summary

1. Histoplasmin skin tests have been performed on 75 children from a small city located 30 miles from Montreal, Quebec. These were done concurrently with tuberculin tests. Chest X-rays were taken of those positive to both tests.

2. Twenty children were positive to histoplasmin, of whom 10 were also positive to tuberculin. No relation was found between histoplasmin and tuberculin reactions.

3. Nine subjects were shown to present pulmonary calcifications, of whom 3 were negative to tuberculin.

4. The authors outline the importance of these first results and propose to carry on more extensive histoplasmin surveys in other parts of the Province of Quebec, supplemented by serologic tests and research in domestic and wild animals.

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Cyanosis of Infants Produced by High Nitrate Concentration in Rural Waters of Saskatchewan

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Regina

A NUMBER of papers (1-6) in the medical literature of the past few years have drawn attention to cases of cyanosis in infants, attributable to nitrates contained in the water used to make up their formulae. The ingested nitrates are apparently reduced to nitrites in the gastro-intestinal tract, with the nitrites absorbed into the blood stream to combine with haemoglobin forming methaemoglobin. Methaemoglobin is incapable of carrying oxygen. The oxygen-carrying capacity of the blood may be so reduced that anoxemia and cyanosis appears. The anoxemia so produced may be mild, serious or fatal, depending on the proportion of total haemoglobin that has been inactivated as methaemoglobin.

The recognition that nitrate-bearing waters might play a significant role in the production of cyanosis in infants emphasized the need for an estimate of the prevalence of such waters. If the proportion of drinking waters that contained significant amounts of nitrates could be estimated, the extent of the hazard could be judged to determine if routine nitrate estimations on drinking-water supplies were warranted. Such a program of nitrate determinations on all samples of drinking waters submitted by the public for sanitary opinions was begun in May 1948 and has been continued to date.

Nitrates are generally regarded as an end product of bacterial decomposition of animal or vegetable matter. As such, the level of nitrate content is a rough guide to the degree of contamination of a well from these sources. Barnyard pollution of rural wells is not uncommon, either from faulty surface drainage, adjacent watering areas, or poor cover and cribbing on the well itself. Occasionally, bacterial decomposition of the humus of the soil must be suspected as a source of nitrates in some deep drilled wells where there is no obvious source of contamination. However, such contaminated drilled wells are rare. It is the dug wells that are most exposed to contamination.

On the basis of a report of earlier workers (2, 7), the concentration of nitrates in water considered dangerous for infant feeding was at the outset accepted as 20.0 parts per million (p.p.m.).

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[1]*Chief Chemist.* [2]*Director.*

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This project was supported by funds from the Dominion Health Grants.

Analytical Survey

In the period May to November, 1948, more than 2,000 samples of rural drinking waters from different areas were received at the laboratory for a sanitary opinion. This normally requires a bacteriological and mineral examination. Nitrate estimations were carried out as well on these samples. Nitrite estimations were also carried out for the first 1,000 specimens and then discontinued.

Only the results on rural well waters will be reported. Nitrate estimations on the regular routine samples of municipal water supplies of towns and cities are not included. No significant amount of nitrates was detected in any approved, inspected well.

Nitrite estimations were discontinued when found to be consistently negligible by comparison with the nitrate content. Nitrite content of waters rarely exceeded 1.0 p.p.m.

The nitrate estimations were more significant. Almost one third of the rural well waters examined contained more than 10.0 p.p.m., a dangerous amount of nitrate ion. Twenty-five and a half per cent of the waters examined contained more than 20.0 p.p.m. of nitrate ion. These results compare with a similar survey conducted on dug wells in Iowa (7), where 28.9 per cent were found to contain more than 20.0 p.p.m. of nitrates. The complete findings are shown in Table I.

TABLE I

Concentration of Nitrate Ion found	Percentage of rural Saskatchewan Well Waters Examined	Percentage of Iowa Wells Examined (7)
0- 10 p.p.m.	68.6	
10- 20 p.p.m.	5.9	
20- 50 p.p.m.	6.7	13.6
50-300 p.p.m.	13.5	
over 300 p.p.m.	5.3	15.3

As expected, the great majority of "dangerous" waters came from dug wells with obviously inadequate protection. Drilled wells were included in the above survey and their record was much better. However, they did contribute 2.4 per cent of the dangerous nitrate waters received. Two of these drilled wells were found to be contaminated from adjacent subsurface sewage disposal areas. The sewage seeped down alongside the pipe casing to the bottom of the well and thence to the water supply. It is the other "dangerous" drilled wells with good protection that suggest the possibility of bacterial decomposition of humus layers of the soil as a source of nitrates.

Coliform Organisms: Because nitrates and coliform organisms contaminating a water might possibly originate from the same source, a comparison of the nitrate content with presence or absence of coliform organisms was carried out on the same samples.

A review of Table II shows that a rough parallel does exist. At low nitrate concentrations, coliforms may or may not be present. With increasing levels of nitrate content and hence increasing pollution, the percentage of such waters that also contain coliforms increased. Seventy per cent of all waters containing more than 50.0 p.p.m. of nitrates also contained coliform organisms.

TABLE II

RANGE OF NITRATE CONTENT

	0-10 p.p.m.	10-50 p.p.m.	50-300 p.p.m.	More than 300 p.p.m.
Percentage of all rural waters examined	68.6	12.6	13.5	5.3
Percentage of all rural waters found to contain coliform organisms as well	40.2	6.0	9.7	4.1
Coincidence of nitrates and coliforms	58.5	47.6	71.7	77.3

Sixty per cent of all rural waters were unsafe as based on the presence of coliform organisms. This included 19.8 per cent of the total waters examined that were also dangerous because of high nitrate content. However, there was an additional 11.6 per cent of all waters examined that were dangerous because of nitrate content but contained no coliform organisms. Thus 71.6 per cent of rural Saskatchewan well waters examined contained either coliform organisms or dangerous amounts of nitrates, or both. Boiling would render safe for infant feeding all but the 31.4 per cent of such waters that were nitrate-contaminated.

CLINICAL CORRELATION

The significance of high nitrate contents of rural waters used for infant feeding was confirmed by the occurrence of 12 reported cases of cyanosed infants in the Regina area during this six-month period. All of these were suspected methaemoglobinaemias. Ten of the cases were established definitely as such by blood analysis and the responsibility traced to nitrate-contaminated waters used in making up the formulae. The two remaining cases recovered in hospital without therapy before blood samples could be collected to establish the presence or absence of methaemoglobin. In the latter two cases no therapy was attempted other than a formula prepared with nitrate-free water.

Two of the infants cyanosed very rapidly and died en route to the hospital before therapy could be commenced. In all cases, the waters used in the formula contained "dangerous" amounts of nitrate ion. Immediately after the two fatalities referred to above, the physicians were notified by letter of the advisability of having the prospective water supply for an infant's formula tested for nitrate content before needed for such use.

It is probable an equal number of cases were avoided by the ability in many cases to warn the physician beforehand that certain water supplies would be unsuitable for infant feeding because of high nitrate content.

It is certain that at least one life was saved by prompt recognition of the danger and the application of methylene blue therapy. Fifty per cent of this infant's haemoglobin had been converted to methaemoglobin at the time therapy was commenced.

A full account of the two fatalities which were reported and came to autopsy is being published elsewhere. There was little clinical warning in either case. The development of cyanosis was relatively sudden.

Case 1. Baby B.—boy.
Full term—normal delivery.
Formula—lactogen and boiled water.
First symptoms—crying, uneasiness—one evening.
When seen by doctor—cyanotic; crying, respiratory distress.
Therapy—no methylene blue available locally, so rushed by automobile to Regina.
Termination—Death en route to Regina 90 minutes later.
Methaemoglobin—More than 25 per cent of total haemoglobin converted to methaemoglobin.
Analysis of water used in formula—Nitrates 1219.0 p.p.m.
Nitrites 12.6 p.p.m.
Condition of well—deplorable, shallow dug well with poor cover, and every opportunity for barnyard contamination.
Pathologist's report—Methaemoglobinaemia.

Case 2. Baby S.—girl.
Full term—normal delivery.
Formula—first 32 days of life Carnation Milk 6 oz.
Corn syrup 2 tbsp.
Boiled water 15 oz.
Feed 4 oz. O.H.4.
First symptoms noticed by doctor—crossness, sleeplessness, on one occasion dull and indifferent; formula changed to:
Lactogen 2 tsp.
Boiled water 4 oz.
Feed 4 oz. O.H.3.
Termination—Improvement for 4 days. Then sudden distress, cyanosis, and prostration. Died en route to Regina Hospital.
Methaemoglobin—(autopsy) 44 per cent of total haemoglobin combined as methaemoglobin.
Analysis of water used in formula—Nitrates 1320 p.p.m.
Condition of well—deplorable, shallow dug well with pump supplying barnyard, but little or no protection from barnyard. Evidence about of such contamination.
Pathologist's Report—Methaemoglobinaemia.

It will be noticed that both infants were on powdered-milk formulae at time of death. The waters used to make up the formulae contained 1219 and 1320 p.p.m. of nitrate ion, respectively. This would correspond to an intake of about 1000 milligrams of nitrate ion per day or 220 milligrams of nitrate ion per kilogram of body weight. Both wells were inspected and found in a shameful state of neglect; poor covers, drainage and protection were the rule, with evidence of animal excreta all about the well and on the well covers.

Seven other infants from rural areas developed cyanosis and were admitted to hospital as suspected cases of methaemoglobinaemia. The waters used in their formulae were secured and analyzed for nitrate content. All such waters possessed more than 75.0 p.p.m. of nitrates. Blood samples taken from this group

all contained methaemoglobin in amount varying from 5 to 50 per cent of the total haemoglobin. In general, cyanosis was first noticeable when 10 per cent of the haemoglobin was in the form of methaemoglobin. Cyanosis was severe with 20 per cent methaemoglobin and fatal in one case with 44 per cent methaemoglobin. However, one infant admitted to hospital in respiratory distress was found to contain 50 per cent of total haemoglobin in the form of methaemoglobin. Prompt intravenous administration of 2.0 ml. of 1 per cent solution of methylene blue resulted in complete disappearance of the cyanosis and distress within 30 minutes.

Generally, adequate therapy consisted of adopting the use of a safe water supply for use in the formulae. In the two most serious cases methylene blue was used intravenously. The recovery was dramatic. In some cases that were hospitalized in late evening, samples of blood drawn the following day showed much less methaemoglobin than would have been expected from the severity of the cyanosis.

The smallest concentration of nitrates in waters observed in this series to produce methaemoglobinaemia in an infant was 75.0 p.p.m., corresponding to a per diem ingestion of nitrate ion of about 41.0 milligrams total or 15 milligrams per kilogram per day. A concentration of 17.5 p.p.m. in one water was suspected of causing cyanosis in an infant, but the infant recovered so rapidly in hospital on a "safe" formula that the following day there was less than 5 per cent methaemoglobin in the blood. This would correspond to an oral ingestion of about 15.0 milligrams total per day or 4.0 milligrams per kilogram of body weight per day.

Discussion

It is the total amount of nitrate ion that might be ingested by an infant that must be considered in advising if such a water is safe or dangerous because of its nitrate content. The analyst cannot tell at a distance how much water will be consumed in a formula per day, so such recommendations must be based on the maximum amount that might be ingested by a 3-month infant on a powdered milk formula. If this be of the order of 35 oz., then our experience has definitely shown that this volume of water should contain less than 41.0 milligrams of nitrates or a concentration considerably less than 41.0 p.p.m. Our experience has thrown suspicion on a water that contributed 15.0 milligrams per day of nitrate ion, which would correspond to a concentration of 15.0 p.p.m. of nitrates. This supports the recommendations of the Iowa workers (2, 7) that waters containing more than 10.0 p.p.m. of nitrate ion should be avoided if possible for infant feeding. Those containing more than 20.0 p.p.m. of nitrates should be definitely avoided.

Whether or not an infant will develop methaemoglobinaemia from ingestion of a nitrate water depends on several other factors in addition to the absolute amount of nitrate. Firstly, in order to provoke methaemoglobinaemia and in order that the nitrites can be absorbed into the blood stream, the nitrate must be reduced to nitrite at an early stage, in the gastro-intestinal tract. This requires the presence of nitrite-reducing bacteria in the upper gastro-intestinal tract. As

Cornblath and Hartmann (6) have demonstrated, gastric acidity determines whether or not nitrite-reducing bacteria will thrive in this area. They state that only infants who have a gastric pH higher than 4.0 and nitrate-reducing bacteria in the upper gastro-intestinal tract ever develop methaemoglobinaemia from oral ingestion of waters containing nitrates.

Another factor is the energy of the enzyme system generally operating within the red blood cells to reduce methaemoglobin back to haemoglobin. The two fatalities observed suggest this enzyme system may collapse rather suddenly.

The total amount of haemoglobin originally present also must be important, for it would bear on the amount of methaemoglobin that could be tolerated before the anoxemia would become serious.

Summary

1. About one third of the rural wells of Saskatchewan contain sufficient amounts of nitrate ion to be dangerous if used in infant formulae. Barnyard contamination of the dug wells is the most common source of this nitrate. The presence of coliform organisms in the majority of such nitrate waters supports this view.

2. Ten cases of methaemoglobinaemia of infants have been identified with high nitrate waters used in formulae. Two fatalities occurred from this cause.

3. Treatment of choice has been the use of a safe water supply in the infant's formula for all cases; in the severe cases, methylene blue intravenously—2 ml. of a 1 per cent solution.

4. A complete sanitary opinion of a drinking water should include a reference to nitrate content.

ACKNOWLEDGMENTS

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Two Years' Experience with Delayed Gonococcus Cultures

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THE bacteriological diagnosis of gonorrhoea in males by microscopic examination is generally accepted as satisfactory; but this same examination, when applied to female patients, has been found to be inadequate. During the first six months of 1945, 11,890 smears were examined, as an aid in the diagnosis of gonorrhoea, by the Division of Laboratories of the Quebec Ministry of Health. The male specimens numbered 3,430 with 33 per cent positive, whereas the female specimens, numbering 8,460, gave a positivity rate of only 5 per cent.

Though well aware of the superiority of cultural methods over microscopic examination, central laboratories were slow in adopting these methods because of the lack of satisfactory means of transmitting specimens by mail. In a study of different carrying media, Coleman and Clark (1, 2) concluded that Hirschberg's medium (3, 4) is both efficient and practical. Daily use of this medium for the last two years has led us to confirm this conclusion. A study of the results obtained from delayed cultures, as compared with direct cultures and microscopic examinations, is the subject of this report.

Method

In a previous paper (5), we have described the procedures used in the collection of exudates. One point to be emphasized is that the success of this delayed culture method depends, in great part, on the care of the operator when collecting the secretions.

Hirschberg's medium is a coagulated blood-gelatin agar. It consists of agar, 20; gelatin, 40; sodium chloride, 5; disodium phosphate, 5; peptone (Difco proteose No. 3), 20; glucose, 0.5; and distilled water to make 1,000 grams. This agar base is adjusted to pH 7.4-7.6 and autoclaved 20 minutes at 15 lbs.

To the melted agar base is added defibrinated sterile sheep blood in the proportion of 20 ml. of blood to 80 ml. of base at a temperature of 85° to 90°C. The complete medium is rapidly dispensed in 5-6 ml. amounts in sterile test tubes (5 × 5/8 in.) stoppered with paraffined corks.

This carrying medium is essentially the one used by the New York State Division of Laboratories and Research. Two minor modifications have been

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introduced: for convenience, sheep blood is used instead of horse blood, and Nile Blue A is omitted because we have detected no advantage in its use.

The mailing outfit employed comprises two tubes containing the carrying media, labelled "C" for cervix and "U" for urethra, two glass slides and four sterile swabs. These swabs are used for the collection of secretions for cultures and the preparation of films. Swabs intended for cultures must be thrust into the medium and left there until the outfit reaches the laboratory. Upon reception, the swabs are smeared on a chocolate agar: Bacto-Proteose No. 3 agar enriched with Bacto-Hemoglobin and Bacto-Supplement A (yeast concentrate, crystal violet 1:6000). In January, 1948, Bacto G.C. Medium base (6) was substituted for Bacto-Proteose No. 3 agar. The use of the former medium, containing starch, is preferable because it furnishes a satisfactory result after the relatively short interval of twenty-four hours. The plates, contained in an ordinary paint can with tight-fitting cover, are incubated at 36°C. An atmosphere of carbon dioxide is supplied by a lighted smokeless candle.

The procedure followed in the examination of plates is essentially the one recommended by Carpenter (7). This examination can be divided into three separate operations: first, observation of typical colonies by macroscopic examination; second, flooding the plates with a one per cent aqueous solution of p-Aminodemethylaniline Monohydrochloride; third, a search for the presence of gram-negative diplococci in smears from pink colonies. In the routine diagnosis of gonorrhoea these operations are considered sufficiently accurate for the identification of the gonococcus.

However, in certain instances, when the source of the specimen is not the genito-urinary tract, when a medico-legal question arises or when a treated case is repeatedly positive, the suspected organism is isolated in pure culture and tested in carbohydrate media for final identification. A starch-gelatin agar recommended by Spencer and Wallace (8) has been found satisfactory for the determination of fermentative properties.

Results

To investigate the reliability of Hirschberg's medium, as used in our laboratory, a preliminary study comparing results of direct and delayed cultures was initiated. Ninety specimens from female patients treated in a local clinic were examined. Delays between collection of secretions and the preparation of plate cultures varied from 4 to 12 hours. The findings may be summarized as follows: films, 7 positive (8 per cent); delayed cultures, 22 positive (24 per cent); and direct cultures, 28 positive (31 per cent). In 5 instances of doubtful results by microscopic examination, 3 positives and 2 negatives were obtained after cultural study.

Following this experience, delayed cultures were offered as a routine service by our laboratory. From October, 1946, to September, 1948, a total of 4,230 female patients' specimens were received for film examinations and delayed cultures. Time elapsing between the collection of exudates and preparation of the cultures varied from 4 to 48 hours. Although the majority of these specimens

came from Montreal, an appreciable number were shipped by mail from distances up to 400 miles.

Four types of reports on miscoscopic slide examinations are issued. These reports are essentially as follows: 1. Negative: No gonococci. No pus cells. 2. Negative: No gonococci. Few, or many pus cells. 3. Doubtful: Pus cells, gram-negative extracellular diplococci. 4. Positive: Typical intracellular gram-negative diplococci.

From the 4,230 specimens examined, 121 or 3 per cent were found positive by slide examination and 553 or 13 per cent gave positive results by the delayed culture method. An interesting feature is the results of the slide examination of specimens corresponding to these 554 positive cultures. Results were negative in 64 specimens or 11 per cent; pus cells only were found in 330 specimens or 60 per cent; the result was termed doubtful in 60 specimens or 11 per cent; and in 99 specimens, or 18 per cent, the result was positive. The total number of doubtful slide results was 280; of these, 60 became positive when cultured and 220 remained negative. In this study, gonococci were found both by smears and cultures in 99 cases; by cultures only, in 454 cases; and by smears only, in 22 cases.

As might be expected, specimens from venereal disease clinics yielded a much greater proportion of positive cultures than did those from institutions engaged in the routine detection of infection. For instance, 250 specimens from a local V.D. clinic gave 80 positive cultures, or 32 per cent, and only 6 positive slides, or 2.5 per cent. Of 1,262 specimens from an institution 4 per cent were positive by slide examination and 9 per cent by cultural methods.

Summary and Conclusions

The detection of gonococci by microscopic slide examination of specimens from female patients is subject to serious limitations. Since cultural examination of specimens is definitely recognized to give superior results, the establishment of a gonococcus culture service was indicated. Consequently, a carrying medium, a coagulated-blood gelatin agar described by Hirschberg, for maintaining satisfactory viability of the gonococcus for at least 48 hours, was investigated. A preliminary comparative study of direct and delayed cultures showed that direct cultures were slightly superior to delayed cultures.

A study of 4,230 duplicate specimens, for microscopic examination and delayed culture, resulted in a decided advantage in favor of the delayed culture, culture yielding a 13 per cent positivity rate whereas the microscopic examination showed only 3 per cent positive.

The cultural examination of specimens giving doubtful results by smear examination indicated that, although the majority were indeed negative (78 per cent), an appreciable number were found to be positive (22 per cent).

Specimens from venereal disease clinics yielded a much greater proportion of positives than did those from institutions. The positivity rates obtained from these clinic specimens compare favorably with those usually obtained by direct examination of smears from male patients.

These results confirm the contention that Hirschberg's medium is a reliable carrying medium for delayed gonococcus cultures. As its efficacy is not perfect, the additional miscoscopic examination of smears is still desirable. The latter will detect the odd strain unable to survive or to grow on our media and will also serve as a control of the reliability of our cultural methods.

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SUMMER INTERNSHIPS IN PUBLIC HEALTH

IN this issue an account is recorded of the work and impressions of a member of the graduating class in the Faculty of Medicine, University of Toronto, who spent last summer as an "intern" in the East York—Leaside Health Unit serving a suburb of Toronto. In this article Mr. Rapoport points out that the purpose of the internship is "to supplement the theoretical teaching in preventive medicine by practical field work in order to develop an attitude of mind valuable to the physician, regardless of the branch of medicine he may choose." He proved himself to be a keen observer and his report is of real interest.

Quite aside from the purpose which he mentioned is the possible value of this plan as a means of interesting a number of those who are graduating in considering public health as a career. It is not necessary to stress the fact that there is an urgent need for physicians with public health training to make possible the extension of full-time health services in all Provinces. Of the physicians returning from the Services, more than two hundred undertook postgraduate training and many of them are now directing local public health programs. While this was very encouraging, the attractiveness of opportunities to engage in practice, the shortage of physicians in many areas, and the much greater financial returns of practice, have drawn some public health physicians into practice and have also seriously reduced the number of physicians who, after practising for a few years, have proceeded with postgraduate training and entered public health as a career. The situation is critical. Public health is part of the field of medicine and its responsibilities are continuously being increased. Summer internship for senior medical students might well be considered by all provincial departments of health not only for its fundamental value to the future practitioner, but also as a possible means of enlisting promising graduates in public health. The Province of Ontario is to be congratulated on its action this year in providing internships for as many senior students as desire to engage in this work. Eleven internships have now been arranged for the coming summer. The provision of these internships can be made possible in all the Provinces through the professional training grants provided from the National Health Grants of the Federal Government. The returns will be out of all proportion to the amount of money involved.

Such an internship is not as novel as it may seem. Camsi, the Canadian Association of Medical Students and Interns, which has made such a splendid contribution to medical education, is providing a service for obtaining summer work. The main objects are twofold: to supply clinical-year students with the opportunity to spend the summer with a practising physician, and to show students the true status of the general practitioner—"not a day-in, day-out, slugging job, but rather an exciting adventure in living." This year, the project has been started early so that the lists of opportunities may be available in time to permit of adequate planning. Internships in public health may well prove to be a step of great importance in meeting the need, ultimately, of more physicians to enter the field of public health.

HISTOPLASMOSIS

HISTOPLASMOSIS has been recognized clinically for a number of years, cases having first been described in 1906 by Darling.[1] The clinical manifestations of the severe infections include an irregular, low-grade fever, and enlargement of the liver and spleen, with anaemia and leucopenia. Frequently there are symptoms of pulmonary infection, pleural pain, cough and expectoration. Symptoms referable to ulcerated lesions of the gastro-intestinal tract are also included. The duration of the disease is from a few weeks to many years, and the diagnosis has been established by adequate cultural techniques and the examination of biopsy material. The geographic distribution indicates a wide variation in prevalence as determined by sensitivity tests. An observation of very great interest made by Palmer[2] and by Peterson and Christie,[3] indicated that histoplasmin sensitivity is much more prevalent in areas where chest X-ray examinations show a prevalence of pulmonary calcifications. It is suggested that there is an intimate relationship between the incidence of pulmonary calcifications and histoplasmin sensitivity. Histoplasmin sensitivity varies greatly with geographic areas. Peterson and Christie state: "It is apparent that the question of histoplasmin sensitivity and its relation to pulmonary calcifications is one which may be of great importance in one locality and of no importance in another; and also that some factors of climate and physical geography must be of great significance in the epidemiology of histoplasmosis. There is an increasing percentage of reactors in childhood with increasing years."

The first studies in this field in Canada are reported in this issue by Guy, Roy, Poupart and Panisset. Further work is being carried forward by these authors and more extensive histoplasmin surveys are being planned in other areas in the Province of Quebec.

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Pioneers in Public Health*

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ALTHOUGH the important work of the public health officer lacks the glamour of surgery and some of the medical specialties, and is also devoid of the intimate relationship between the family physician and his patients, yet he deserves the gratitude of all, and a little memoir of some of the pioneers may be of interest.

Frederick Montizambert, M.D., C.M.G.

When Sir John A. Macdonald appointed Dr. Frederick Montizambert Director General of Public Health he became the first quarantine officer after Confederation. During his long tenure of office, Dr. Montizambert was the leading health official in Canada, and he was awarded a C.M.G. for his services to the Dominion. At international health congresses he always represented Canada, and none could do it better. The fact that at one time he was president of the American Public Health Association is a proof of the American's high regard for him.

Dr. Montizambert was an aristocrat, due to his lineage from an old Quebec family. His tall, handsome appearance and general bearing and way of life daily confirmed this. If he seemed somewhat aloof and lacking in the free-and-easy manner of the general run of health officers, further acquaintance proved him to be most friendly and helpful, for he was blessed with fine judgment and was always a gentleman.

In his daily appearance on the street, he was not infrequently taken for the Duke of Connaught, whom he resembled in many ways, and with whom he was on very friendly terms. Once while he was walking past the old fort in Quebec City, the guard, thinking he was the Governor-General, turned out and saluted him.

As did these soldiers, thinking he was the Duke, so may we, knowing him as he was, stand at salute to his memory—our first pioneer public health officer.

Peter H. Bryce, M.A., M.B.

Dr. Peter H. Bryce, first secretary of the first Provincial Board of Health of Ontario which was established by the Public Health Act of 1882, was just the opposite type to Dr. Montizambert. Enthusiastic to a marked degree, and a strenuous worker, he was always bubbling over with schemes for improving sanitation.

He was especially interested in the tuberculosis problem. In fact, he installed a tent for a tuberculous Indian out on the Mohawk Reserve near Brantford, but whether the Indian occupied it much of the time may be doubted. But this act showed Dr. Bryce's spirit, and it also showed up the spirit of public indifference towards this problem—an apathy that was transformed into action for betterment of conditions by the great and lasting work of Sir William Gage.

It may be of interest that Dr. Bryce, a great friend of Mr. Woodsworth, who later became leader of the Canadian Commonwealth Federation, tried to secure for him a position with the Canadian Tuberculosis Association, as he was then seeking some suitable position. Being then very low in funds, the Association

**From time to time it is purposed to present, under this heading, excerpts from addresses and short articles on the history of public health. It is pleasing that the first article in this series is by Dr. George D. Porter, a pioneer in public health whose contribution to the tuberculosis control program will always be remembered.*

was unable to consider it, thus leaving Mr. Woodsworth an open road towards the much wider field of Canadian politics.

Dr. Bryce made one attempt at lighter literature than sanitation and wrote a short novel whose hero discussed social problems from the author's viewpoint. But one fears that the novel-reading public did not enthuse over it, for public health lacks the dramatic and other essentials desired by most of of them. At any rate, no second edition appeared.

In 1903, Dr. Bryce resigned as Chief Health Officer, to accept the appointment as Chief Medical Officer in the Department of Immigration, Ottawa. The progress made by the Provincial Board of Health during the first thirteen years of its existence was due largely to the efforts of Dr. Bryce. The formation of local boards of health was stimulated, and assistance given them in the control of outbreaks of disease. Important public health legislation was enacted, a bacteriological laboratory was established, and a system of vital statistics was set up.

While the modern graduate in public health might smile at the extent of the staff and facilities of the department of which he was secretary, it would prove no handicap to health officers today to have some of the enthusiasm and vigour displayed by our old friendly pioneer, Dr. Peter Bryce.

Maurice M. Seymour, M.D., D.P.H.

Dr. Maurice M. Seymour, the first Commissioner of Public Health in Saskatchewan, in 1906, was a most energetic worker for the betterment of the people's health in his province. One trait of his character was that he sought outside as well as inside advice, and welcomed experts where needed and always made good use of them. Wisely, he placed emphasis on improving sanitary conditions, and had the advice of T. Aird Murray, an engineer of wide experience, in studying the supply of safe water and the disposal of sewage. The problem was no small one, but he made great strides in improving conditions.

His greatest interest was for the care of the tuberculous and in methods towards the control and prevention of this widespread disease. Forty years ago there was no provision for the tuberculous in Saskatchewan, and his first objective was to have a sanatorium. To arouse public interest and support he got outside help, and lectures were delivered all through the province. Local societies were formed, and then a provincial one. Together with the Government, they erected a fine sanatorium at Fort Qu'Appelle, and later on, others near Saskatoon and Prince Albert. Modern preventive measures against tuberculosis went hand in hand with these, and as a result Saskatchewan has lowered its death rate from tuberculosis to a remarkable degree. Later, he established a system of municipal hospitals for Saskatchewan which proved to be practical and of great value.

Charles A. Hodgetts, M.D., L.R.C.P.(Lond.), F.R.S.I.

Dr. Charles A. Hodgetts, who succeeded Dr. Bryce as Chief Health Officer for Ontario in 1903, has had a most varied experience in public life. His training at home must have favoured a methodical and efficient way of doing things, and he proved equal to the many positions he occupied. In this regard, his virtuosity was remarkable.

While Chief Health Officer, among other accomplishments he got together a fine travelling tuberculosis exhibit, the first of its kind in Canada. This was shown in many centres, where helpful public addresses on the subject were given by various medical men.

On the formation of the Conservation Commission in 1910, he was called to Ottawa to become its medical adviser. Among other health matters, he was greatly interested in housing and he travelled extensively in Europe to study conditions there.

When World War I broke out, he

went overseas as Chief Commissioner of the Canadian Red Cross Society, in which capacity he served until near the close, when he was appointed assistant commissioner for the British Ministry of National Services for Ireland, with headquarters in Dublin. For his war work he was mentioned in despatches and decorated by the British, Italian, and Belgian governments.

Colonel Hodgetts made a great contribution to the work of the St. John Ambulance Association. For many years he was honorary secretary of the Dominion Council of that organization. On returning to Canada after the war, he resumed the duties of honorary secretary and later was appointed director-general, in which position he served until he resigned in 1932.

Nearly ninety years of age, Dr. Hodgetts is now resident in Vancouver and continues his interest in the progress of public health and in the work of the St. John Ambulance Association. It was pleasing that he participated in the annual meeting of the Canadian Public Health Association, held in Vancouver last May, when he was honoured as the first president of the Association under its Dominion charter.

Dr. Hodgetts has a personality which enabled him to get things done without friction. While he fitted into the various positions he held like a hand into a well-fitting glove, he is no "smoothie" — as an occasional opponent may remember. But a ready smile and a handclasp were always in the offing. It is pleasing to know that his work has been appreciated, as evidenced by the many awards and honours which he has received.

HOTEL RESERVATIONS FOR THE 37th ANNUAL MEETING

HALIFAX, JUNE 28-30, 1949

(Executive Council June 27)

Early reservations are essential, as hotel accommodation is at a premium. Requests for reservations must be made through the chairman of the Committee on Reservations, Dr. D. J. Mackenzie, Public Health Laboratory, Morris Street, Halifax. The coupon on page 13 is for your convenience.

	Single Rooms	Double Rooms	Triple Rooms
Nova Scotian	—	$9.00	$10.50
Lord Nelson	$5.00	8.00	10.50
Carleton	—	6.50	8.50

Summer Internship in a Health Unit

A. RAPOPORT

University of Toronto—1949

LAST summer a public health internship was provided for an undergraduate medical student as an experiment in the teaching of public health. The Board of Health of the East York-Leaside Health Unit in suburban Toronto offered a fellowship for this purpose. The project was sponsored by Dr. Milton H. Brown, Professor of Hygiene and Preventive Medicine, University of Toronto, and was under the direction of Dr. William Mosley, Medical Officer of Health of East York and Leaside, and his assistant, Dr. J. M. Parker. An opportunity was thus created for a student to observe and participate in the efforts of a local health unit to maintain the health of a community. Although East York-Leaside is the demonstration health unit associated with the School of Hygiene at the University of Toronto, its program is much the same as that of the twenty-odd health units throughout Ontario. It is hoped that similar internships will be available in several Ontario health units next summer.

While some of the students who undertake this work may proceed to a career in public health, they are under no such obligation, and this internship is not regarded primarily as a recruitment program for public health officers. Its purpose is, rather, to supplement theoretical teaching in preventive medicine by practical field work, in order to develop an attitude of mind valuable to the future physician regardless of the branch of medicine he may choose. This attitude may be described as a sort of medical "view-of-life", in which preventive medicine is seen in relation to the general welfare not only of individuals but also of communities and nations; and in which health is viewed not merely as the negation of illness but as a positive attainment in itself. More specifically, the student will learn the many ways in which the local health department can be of use to the practising physician, and how the physician can co-operate in turn to raise health standards.

So that the student would share in the work of the unit, as well as observe its activities, the director devised two projects for him. The first was to survey the active tuberculosis cases of the Unit. By examining the records he was to ascertain how many patients were found by strict epidemiological measures such as tracing contacts, as opposed to those learned of by more "shot-gun" methods such as mass surveys. The results are perhaps sufficiently interesting to note here. Of 328 active tuberculosis cases, only 28 had previously been listed as contacts. Three hundred, therefore, had been detected by other methods. This illustrates the limitations of a purely epidemiological approach to the problem of tuberculosis detection and stresses the need for mass surveys. Furthermore, only 66 of the patients could list a possible source, and many of these were so remote as to preclude all chance of infection originating from them. This fact points to the necessity for more exact definition of how intimate a relationship constitutes a source or a contact, and emphasizes again the great gaps in our knowledge of the epidemiology of tuberculosis.

From this study the student also became familiar with the intermediate stages in tuberculosis statistics, from the private physician to the Provincial Government, and with the

This article, written primarily for The University of Toronto Medical Journal, is published here because of its interest for those engaged in public health.

extensive correspondence involved in tracing contacts and admitting patients to sanatoria. Visits made to the homes of sanatorium patients very forcefully demonstrated that the familial and social environment of a patient must not be overlooked when prescribing treatment. One can imagine the distress of an invalid in sanatorium, burdened with problems of raising money to pay for his treatment and upkeep there and for the maintenance of his family at home. Fortunately, voluntary tuberculosis associations and provincial governments now cover most of the costs of sanatorium care and make provision for the families of tuberculosis patients. This broader view of therapy can perhaps be better evaluated in a health unit, where homes are visited and family tensions witnessed, than in a hospital where the patient is a "case" occupying a bed and seemingly divorced from his surroundings.

The second task was to survey by home visits some of those houses in East York which had not installed plumbing and sewage facilities. Data were collected on the condition of the house, the number of rooms, and the condition of whatever means of sewage disposal were available. It will come as no surprise that most of these homes were in the poorer section of the Township. This study was invaluable for demonstrating the social and economic forces which influence the health program of an area and which must be contended with if such a program is to be fully successful.

Tours made with the two sanitary inspectors of the unit were very revealing. These included routine inspection of swimming pools, restaurants, and food and packing plants. Many trips were made to investigate "nuisance" complaints. These ranged from the keeping of pets by neighbours to soiling of the dwelling by the children of tenants. One could not help but be astonished, in certain cases, at the solicitude shown for community health by some plaintiffs whose own properties were anything but clean.

Visits made with the public health nurses were equally significant and more provocative of human interest. There are twelve nurses on the health unit staff. All mothers in the area are visited about a month after delivery and given advice as to the care of the infants. They are also encouraged to attend the child health centres and immunization clinics sponsored by the unit. A large part of the nurses' work relates to the tuberculosis program, and the moving drama of the disruption of family life due to this disease has already been suggested. Random visits — such as inspecting a house to determine its suitability as a boarding home for children, or calling on a lonely old-age pensioner with no family, to assure her that someone still is concerned with her well-being—likewise showed how sociology may help us to see medical practice in a new light and more fully exploit its possibilities as an instrument of social welfare.

A more or less regular event was the weekly afternoon visit to the child health centre, known more colloquially as the well-baby clinic. Here a physician, with the assistance of nurses and volunteer workers, gave physical examinations to babies brought in for the first time, adjusted formulae as required, and noted the progress of the infants in weight and appearance. When treatment was required, the mother was referred to her family physician. This action is in keeping with the policy of the health unit of not competing with the local physicians but, rather, of assisting them and complementing their services. Physicians in practice not only are encouraged to co-operate with the unit, but in certain instances are engaged to help perform its functions.

Among the most fruitful experiences of the summer were the discussions held at the office by the staff, visiting health officers, and welfare officials.

In these the pros and cons of a host of issues, medical and otherwise, were thrashed out. By taking part in such discussions, one gathers a great deal of information, appreciates different points of view, encounters new ideas, and acquires a deeper understanding of fundamental problems of health and disease.

This has been in no way an exhaustive description of the many-sided activities of a health unit. Rather, an attempt has been made to depict, for those students who may be interested, the goals and offerings of a new type of internship which the author found both profitable and pleasant.

NEWS

Canadian Tumour Registry

A CENTRAL TUMOUR REGISTRY is being established at the federal Laboratory of Hygiene, Ottawa, to assist in the general program of the National Cancer Institute of Canada. The government has approved expenditures for the creation and functioning of the registry, which will provide scientific facilities for the campaign against cancer. Staff is now being appointed, and equipment and supplies are on order.

The National Cancer Institute of Canada has named Dr. Desmond Magner, professor of pathology at the University of Ottawa, as registrar of the new establishment. The Department of National Health and Welfare is making available the services of Dr. H. A. Ansley, assistant director of health services, and Mr. James Gibbard, B.S.A., M.Sc., chief of the Laboratory of Hygiene, who will be associated with Dr. Magner in administering the registry. In addition to other work in this field, the registry will assist pathologists in the classification of various cancers and other tumours and will collect case histories and other relative data for future studies. A panel of leading consultants from various parts of Canada has been appointed to act as a technical group for the classification of tumours.

Dairy and Food Inspectors' and Sanitarians' School

THE SIXTH ANNUAL Dairy and Food Inspectors' and Sanitarians' School will be held at Michigan State College April 4th to 7th. Full details of the School and a copy of the program may be obtained by writing Dr. W. L. Mallman, Department of Bacteriology and Public Health, Michigan State College, Lansing, Mich.

British Columbia

THE BRITISH COLUMBIA DIVISION of the Canadian Arthritis and Rheumatic Society is going ahead with a plan for treatment and research, subject to the approval of the B.C. Government. The plan includes centres for research and diagnosis, a rheumatic fever clinic at the Vancouver General Hospital, mobile physiotherapy units, and special diagnostic and therapeutic facilities for general practitioners throughout the Province.

MISS JEAN GILLIES, formerly with the Division of Venereal Disease Control, has been appointed research assistant to the director of health studies. Miss Joan List has been named to the staff of the Health Education Division.

TEN SANITARY INSPECTORS have been appointed since September 1948 to serve in local public health districts throughout British Columbia. F. R. Alcock, of Vancouver, is employed at Kelowna; L. W. Eckford of Victoria, at Saanich and South Vancouver Island Health Unit; W. J. Armstrong, formerly of North Battleford, Saskatchewan, at Cranbrook; E. B. Harris, formerly of Sarnia, Ontario, at Kimberley; N. Stephenson, from Vancouver, at Trail; A. E. Hill, from Moose Jaw, at Salmon Arm; C. F. Hartigan, from Rosetown, Saskatchewan, at Penticton; J. F. V. Webb, from Calgary, Alberta, at Cloverdale; T. H. Mayoh from Prince Rupert, B.C., at Smithers; H. G. Burke, from Owen Sound, Ontario, at Dawson Creek. All of the above appointments have been made possible through the National Health Grants.

SEVEN ADDITIONAL public health nurses have been placed in communities in

British Columbia through the support accorded by the federal public health grants. This brings to 107 the number of public health nurses serving in districts outside Victoria and Greater Victoria.

EQUIPMENT for local health services is being obtained through funds from the federal health grants. Included in the list are refrigerators, audiometers, illuminated vision testing charts, blood pressure instruments, auroscope—laryngoscope kits and weight scales. Sound film projectors and film-strip projectors are also being purchased to assist in the educational program.

A CONFERENCE for senior public health nurses was held in Victoria from January 4th to 7th, with twenty nurses in attendance. The program included revision of report forms, talks on new developments in provincial services, and reports and discussions on special projects being conducted by the group.

FOUR STATISTICIANS have been appointed to the staff of the Division of Vital Statistics—Miss Patricia Cowan, Miss Joyce Heywood, Mr. Jack Rowe, and Mr. Robert Travis. Mr. Travis is enrolled at the School of Hygiene, University of Toronto, in the course leading to the Certificate in Public Health. Two members of the group are on loan to the Central Island Health Unit to prepare statistical studies on the Wetzel Grid survey. Later these personnel will assist other local health units in the preparation of statistical data in evaluating health unit programs. At the same time consideration will be given to the large problem of the collection of morbidity statistics throughout the province.

Alberta

THE VULCAN MUNICIPAL HOSPITAL has been declared eligible for a grant under the federal government's program to encourage hospital construction. Under the building plan proposed, the bed capacity will be doubled and an incubator room, separate maternity wing, and offices will be added.

THE STAFF OF THE PROVINCIAL MENTAL HOSPITAL, Ponoka, will be increased by the addition of a clinical director, a director of laboratories, a social worker, and four physiotherapists. An expansion of work is being planned that will place greater emphasis on occupational and recreational therapy as curative techniques.

CANCER PROJECTS already being operated by the province will be assisted by a contribution of federal funds amounting to $125,000. These include the diagnostic clinics in Edmonton and Calgary, an X-ray and radium service, and the payment of hospital and surgical fees when operations are recommended by a diagnostic clinic.

THE STAFF of the Drumheller Health Unit has been increased by the appointment of Dr. G. Rhys Jones, formerly of Brandon, Manitoba, as medical officer of health; Miss Victorine Hachey, R.N., as junior health nurse; and Miss Catherine Campbell as secretary-technician.

DR. MARGARET WEST has been appointed assistant medical health officer for the city of Calgary, succeeding the late Dr. Geraldine Oakley who was medical supervisor of schools.

MR. HUGH BOWNES, sanitary inspector of the Red Deer and Stettler Health Units, has enrolled in a three-month course at the U.S. Public Health Service Field Training Centre, at Topeka, Kansas. He is one of four Alberta men taking the course.

Saskatchewan

THE DEPARTMENT OF PUBLIC HEALTH has established a Crippled Children's Service, as a section of a projected Division of Child and Maternal Hygiene. Mr. Keith Armstrong, formerly director of child welfare in the Saskatchewan Department of Social Welfare, has been appointed assistant director in charge of the Crippled Children's Service.

THE REGIONAL BOARD OF HEALTH, Region No. 3, has decided to establish dental service at public expense for all children to the age of 14, similar in most respects to the dental-health service in Health Region No. 1 (Swift Current), where preventive and remedial care is given 10,000 children under 16 years of age.

THE DEPARTMENT OF PUBLIC HEALTH has published a folder for senior medical students and internes on "Professional Opportunities in Psychiatry," the purpose of which is to interest personnel in available positions in Saskatchewan. The Department has also published a folder on psychiatric services in Saskatchewan for

distribution among medical practitioners.

PROVISION OF DRUGS to old-age pensioners and their dependents and recipients of provincial mothers' allowances, as part of health services given since 1945 at public expense, has recently been limited. Beneficiaries are now required to pay 20 per cent of the cost of drugs, with a few exceptions. The Health Services Planning Commission has ruled out payment for patent medicines altogether.

Manitoba

THE FIRST GRANT for crippled children's work under the national health plan has been approved. It will be used to complete a crippled children's registry begun in 1944 in conjunction with the Junior Red Cross; to establish a panel of doctors to examine children needing care; to provide for a full-time nurse to arrange clinics and make investigations; to give medical examinations and treatment; and to two doctors tions and treatment; and to give two doctors advanced training. It is estimated crippling conditions other than poliomyelitis.

A CHILD GUIDANCE CLINIC will be established to serve suburban Winnipeg with the assistance of federal funds. In addition to working among school children, the clinic's staff will be available to give psychiatric advice to the juvenile court, the family court, child welfare agencies and the family bureau.

STREPTOMYCIN will be made available without charge to all patients in Manitoba's sanatoria who might be benefitted by it.

TREATMENT FACILITIES at the Hospital for Mental Diseases, Selkirk, and at the Manitoba School for Mental Defectives, Portage la Prairie, are to be improved through the purchase of additional medical and occupational training equipment.

THE PURCHASE of 75 incubators with federal funds has been approved. These will be distributed throughout the province, particularly among the smaller hospitals, while some will be available for use in homes. According to surveys, one baby in 20 born in Manitoba is premature and therefore needs skilled care and special equipment to get it through the dangerous early months of life.

Ontario

THE NEW Sudbury General Hospital is the first hospital in Ontario to have its application for financial assistance approved under the federal health plan. It will have 165 beds and will be completely equipped for the care of medical, surgical, and maternity cases.

DR. J. P. WELLS, D.P.H., has been appointed director and medical officer of health of the Prince Edward County Health Unit.

DR. J. S. NELSON has retired after thirty-seven years of service as medical officer of health of Nepean Township. He had been in practice in Nepean since 1909.

Quebec

FOUR MOBILE TUBERCULOSIS clinics will be purchased and equipped for use in the accelerated program to control this disease. These clinics will operate in association with four sanatoria strategically located at Three Rivers, Abitibi, Cartierville, and the county of Roberval.

FEDERAL GRANTS have been approved for the construction of several hospitals. The St. Joseph Sanatorium, Montreal, is to accommodate 450 patients and will be fully equipped for major surgery. The St. Joseph's Hospital for Convalescents, also in Montreal, will have its capacity increased by 120 beds. The other hospitals so aided are the Hospital St. Eusebe de Joliette, which is directed by the Sisters of Providence, and the Hôtel-Dieu de Montmagny at St. Thomas de Montmagny.

New Brunswick

FREE TREATMENT of tuberculosis, including streptomycin for all patients who may benefit from its use, will be extended to cover all types of this disease. Mass X-ray surveys will be continued by the travelling unit in those parts of the province not adjacent to established clinics. A diagnostic clinic is also being planned for Fredericton.

PENICILLIN is to be supplied free of charge for the treatment of venereal disease, whether treatment is given at a clinic or by a private physician. Part of the cost of physicians' fees for treatment of cases outside clinic areas will also be met by the provincial government.

ABSTRACTS

The Uses of DDT in Bug Extermination in Slum Properties

Slum dwellings in Glasgow very heavily infested with bed bugs were treated with DDT and Gammexane with excellent results; in fact, recurrence of infestation after several months was almost entirely absent. In addition to effective insecticides, a number of other factors contributed to the success of the experiment. A team of two highly trained and experienced operators who understood the life history and habits of the bed bug was employed. They also understood the task of obtaining tenant cooperation.

The operators were provided with motor transport for their materials. A small portable petrol-driven compressor unit was used for application of liquids, with a nozzle giving a fine shower spray but not as fine as a mist.

A 5 per cent water emulsion of DDT was found completely effective and avoids the fire risk of the kerosene solution. In some houses a 10 per cent DDT powder was used in addition to solution in dealing with pictures, bedding and some articles of furniture. DDT smoke generators were not found suitable for work in slum properties. Gammexane was as satisfactory as DDT.

Preliminary surveys were made of houses to be treated, and instructions given to the inmates. Care must be taken to avoid contamination of food by the insecticide. With such preparation and equipment a series of tenement houses could be sprayed in a comparatively short time. In application of the spray or powder it was essential that coverage be complete and the quantity used liberal. A prolonged residual effect of the insecticides was evident but no ill effects were noted among humans, either tenants or operators.

A total of 204 apartments were treated and a 3- to 4-month follow-up demonstrated an almost perfect result.

W. C. Gunn, Med. Officer, 1948, **80:** *251.*

Penicillin in Diphtheria

Measurement was made of the penicillin-sensitivity of 284 strains of *C. diphtheriae.* Gravis strains were found to be more resistant than intermedius, which in turn were more resistent than mitis strains. Most of the strains required two or three times as much penicillin for *in-vitro* inhibition as did the standard strain of staphylococcus. These concentrations, however, are readily reached in the body.

Treatment of 65 acute cases of faucial diphtheria including gravis, intermedius and mitis infections, with intramuscular penicillin resulted in persistently negative swabs in 75 per cent within 10 days of starting treatment. In one group of 37 cases treated for only 3 days, 70 per cent were free of the infecting organism within 4 days of the end of treatment. Mitis infections appeared to respond best to penicillin therapy. This clearance rate was much superior to that for cases treated with antitoxin alone, so far as comparison could be made. Penicillin, therefore, apart from any possible clinical benefit, should reduce the risk of cross-infection, shorten the patient's stay in hospital and decrease the number who go on to the carrier state.

Treatment of 31 persistent diphtheria carriers resulted in only 13 successes. Gravis infections accounted for the highest proportion of failures. Removal of diseased tonsils in 5 of the failures resulted in cure of the carrier state. Local treatment by spray of 3 cases of anterior nasal diphtheria satisfied the criterion of cure.

It would appear from this study that it is easier to prevent the development of the carrier state by means of penicillin therapy than to cure the established carrier condition.

Report of a Subcommittee of the Public Health Laboratory Service. Lancet, 1948, **225:** *517.*

A World Influenza Centre

Arising out of discussions held at the International Microbiological Conference in Copenhagen in 1947, a World Influenza Centre supported by the World Health Organization has been established at Hampstead, England, under the direction of Dr. C. H. Andrewes. The purpose is to gather data on the prevalence of influenza and to collect strains for study to determine their immunological and serological types and their globe-trotting behaviour. The success of the centre will depend in part on the cooperation of other countries in collecting information and strains for reference to Hampstead when necessary. In the United States measures for this cooperation are already well advanced.

Lancet, 1948, **255:** *775 (Nov. 13).*